REMARKS

Claims 1-36 and 48-49 are pending in this application. Applicants herewith amends claims 1, 22, 48 and 49 and cancelled claims 20, 21 and 28-36. Accordingly, claims 1-27 and 47 and 48 are pending and subject to examination. Applicants maintain that the amendment do not add any new matter. Claims 6, 7, 9, 10, 13, 17, 19 and 27 have been withdrawn from consideration because they relate to non-elected species. Applicants maintain that the amendments do introduce any new matter.

Rejection under 35 USC Section 112, first paragraph

The Examiner rejected claims 1-5, 8, 11, 12, 14-16, 18, 20-26, 28-33, 36, 48 and 49 under 35 USC 112, first paragraph allegedly because the specification does not reasonably provide for treating the broader disorders characterized by abnormal cell proliferation and/or cell differentiation.

In response, applicants respectfully traverse the Examiner's rejection. Nonetheless, and in order to expedite the issuance of the pending claims, applicants have amended claims 1 and 22 to replace the term "a disorder characterized by abnormal cell-proliferation and/or cell-differentiation" with --lung cancer and leukemia--. In addition, Applicants have amended claim 47 to specify that the cancer is lung cancer or leukemia. Accordingly, the Examiner is kindly requested to withdraw this rejection.

Rejection under 35 USC Section 102(b)

The Examiner rejected claims 1-5, 20-26 and 28 under 35 USC 102(b) as being anticipated by Gudas et al. (US Patent No. 5,786,391). The Examiner stated that Gudas discloses

all-trans 4-oxo-retinol as being used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of leukemias as well as lymphomas and squamous cell carcinomas. The Examiner further alleged that the addition of growth factor therapy agent is taught at column 16, lines 64-67. The Examiner further stated that growth factor therapy agents can be interpreted to include inhibitors of growth factor receptors, as shown by Adams et al (US Patent No. 5,864,036;) where novel substituted imidazoles are used in therapy as cytokine inhibitors by inhibiting the epidermal growth factor receptor (EGFR) (abstract and column 36, lines 24-27).

In response, applicants respectfully traverse the Examiner's rejection. Gudas et al. discloses the use of 4-oxo-retinol for inducing differentiation in normal and cancer cells. However, Gudas et al. does not disclose the addition of growth factor receptor inhibitors as the Examiner alleged.

The Examiner pointed to column 16, lines 64-67 to show that Gudas et al. teaches the addition of "growth factor therapy agents". The Examiner relied on Adams et al. (abstract and column 36, lines 24-27) to explain the meaning of "growth factor therapy agents" as including inhibitors of growth factor receptors. Applicants respectfully disagrees.

First, the term "growth factor" but not "growth factor therapy agents" is disclosed by Gudas et al. in column 16, line 67 as a possible combination therapy. Second, Adams et al. does not define any of these two terms. In fact, Adams et al. discloses the use of imidazole compounds to inhibit cytokines and treat cytokine-mediated diseases (column 3, lines 7-11). Adam et al. does not provide a definition of "growth factors" much less a definition of growth

factors that include inhibitors of growth factor receptors. The Examiner's reliance on the abstract and column 36, lines 24-27 to explain the meaning of "growth factors" is inappropriate as no such explanation is provided.

Third, the meaning of the term "growth factors" is well known to persons skilled in the art. Applicants attach herewith attach two publications that defines a growth factor as a serum protein that stimulates cell division when it binds to its cell-surface receptor (see the following web site: http://www.biochem.northwestern.edu/holmgren/Glossary/Definitions/Def-G/growth_factor.html; and http://www.answers.com/topic/growth-factor). Contrary to the teachings of Gudas et al., the present invention relates to the use of growth factor receptor inhibitors as a combination therapy. Therefore, the present invention relates to inhibiting the biological effects of growth factors that are elicited upon binding to their receptors as opposed to the teachings of Gudas et al. of using growth factors to further stimulate biological effects due to binding to the receptors.

In summary, Gudas et does not anticipate the present invention. In fact, Gudas et al. teaches away from the present invention as explained above. Accordingly, the Examiner is kindly requested to withdraw this rejection.

Rejection under 35 USC Section 103

The Examiner rejected claims 1-5, 20-26 and 28 under 35 USC 103 as being unpatentable over Gudas et al. (US Patent No. 5,786,391), in view of Weiner et al. The Examiner further rejected claims 1, 8, 11-12 103 under 35 USC 103 as being unpatentable over Gudas et al. (US Patent No. 5,786,391), in view of Njoroge et al. (US Pub. 2002/0198216). The Examiner further

rejected claims 1, 14-16 and 2932 as being unpatentable under 35 USC 103 over Gudas et al. (US Patent No. 5,786,391), in view of Achkar (US Pub. 2001/0049365). The Examiner also rejected claims 1, 18 and 33 as being unpatentable under 35 USC 103 over Gudas et al. (US Patent No. 5,786,391), in view of Njoroge et al. (US Pub. 2002/0198216). Finally, the Examiner rejected claims 48 and 49 as being unpatentable under 35 USC 103 over Gudas et al. (US Patent No. 5,786,391), in view of Weiner et al. and Njoroge et al. (US PPub. 2002/0198216) and Achkar (US Pub. 2001/0049365).

In response, applicants respectfully traverse the Examiner's rejections. The Examiner is relying on Gudas et al. as a primary reference that teaches the use of certain retinoids in combination with growth factor receptor inhibitors for the treatment of abnormal cell proliferation and/or differentiation. Applicants reiterate the comments made in connection with Gudas et al. above. Accordingly, applicants maintain that Gudas et al. teaches the use of growth factors and not growth factor receptor inhibitors as a combination therapy with 4-oxo-retinol. Furthermore, since the use of growth factor receptor inhibitor has the complete opposite biological result to the use of growth factors, there is no suggestion or motivation to combine Gudas et al. with any reference that teaches the use of growth factor receptor inhibitors. In fact, Gudas et al. teaches away from the present invention.

In summary, none of the other cited references alone or in combination teach or even suggest the combination of 4-oxo-retinol and growth factor receptor inhibitors to treat leukemia and lung cancer. Accordingly, none of the references either alone or in combination render the present invention obvious and the Examiner is kindly requested to withdraw these rejections.

Obviousness-Type Double Patenting

The Examiner rejected claims 1-5, 8, 11, 12, 14-16, 18, 20-26, 28-33, 36, 48 and 49 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-12 of US Patent No. 6,242,435.

In response, applicants respectfully traverse this rejection. The Examiner acknowledged that the US Patent 6,242,435 does not teach the use of growth factor receptor inhibitors. Applicants further reiterate their comments made hereinabove in connection with the 102 and 103 rejections and maintain that none of the cited prior art references either alone or combination teaches the combination of 4-oxo-retinol and growth factor receptor inhibitors like Iressa. In fact, the prior art cited by the Examiner, namely Gudas et al. teaches away from the present invention. Accordingly, the Examiner is kindly requested to withdraw this rejection.

In view of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

Respectfully submitted,

Date: 8/20/2008

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Diane M. Tornali

Dictionary:

growth factor

n.

A substance that affects the growth of a cell or an organism.

growth factor Find

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Sci-Tech Encyclopedia: Growth factor

Any of a group of biologically active poly-peptides which function as hormonelike regulatory signals, controlling the growth and differentiation of responsive cells. Indeed, the distinction between growth factors and hormones is frequently arbitrary and stems more from the manner of their discovery than from a clear difference in function. *See also* Cell differentiation; Hormone.

The sequence of amino acids has been determined for several growth-factor polypeptides. Thisinformation permits a number of growth factors to be placed into families, members of which have related amino acid sequences, suggesting that they evolved from a single ancestral protein. The insulin family comprises somatemedins A and C, insulin, insulinlike growth factor (IGF), and multiplication-stimulating factor (MSF). A second family consists of sarcoma growth factor (SGF), transforming growth factors (TGFs), and epidermal growth factor (EGF). In addition, there are growth factors, such as nerve growth factor (NGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), for which structural homologs have not been identified. *See also* Insulin; Protein.

The stimulation of cell proliferation by several growth factors is similar in some ways to the rapid cell proliferation characteristic of tumor cells. Furthermore, the growth factor receptors are similar to the tumor-causing proteins produced by several RNA tumor viruses. It has been demonstrated that platelet-derived growth factor is virtually identical to the tumor-causingprotein of the RNA tumor virus, simian sarcoma virus. Some forms of cancer involve improper function of growth factors. *See also* Cancer (medicine); Oncology; Tumor viruses.

Dental Dictionary: growth factor

n

One of about a hundred chemical messengers that induces cell growth by tissue type (for example, osteoinductive factor, epidermal growth factors).

Wikipedia: growth factor

The term growth factor refers to a naturally occurring protein capable of stimulating cellular proliferation and cellular differentiation. Growth factors are important for regulating a variety of cellular processes.

Growth factors typically act as signaling molecules between cells. Examples are cytokines and hormones that bind to specific receptors on the surface of their target cells.

They often promote cell differentiation and maturation, which varies between growth factors. For example, bone morphogenic proteins stimulate bone cell differentiation, while vascular endothelial growth factors stimulate blood vessel differentiation.

Growth factors versus cytokines

Growth factor is sometimes used interchangeably among scientists with the term *cytokine*. Historically, cytokines were associated with hematopoietic (blood forming) cells and immune system cells (e.g., lymphocytes and tissue cells from spleen, thymus, and lymph nodes). For the circulatory system and bone marrow in which cells can occur in a liquid suspension and not bound up in solid tissue, it makes sense for them to communicate by soluble, circulating protein molecules. However, as different lines of research converged, it became clear that some of the same signaling proteins the hematopoietic and immune systems used were also being used by all sorts of other cells and tissues, during development and in the mature organism.

While *growth factor* implies a positive effect on cell division, *cytokine* is a neutral term with respect to whether a molecule affects proliferation. In this sense, some cytokines can be growth factors, such as G-CSF and GM-CSF. However, some cytokines have an inhibitory effect on cell growth or proliferation. Yet others, such as Fas ligand are used as "death" signals; they cause target cells to undergo programmed cell death or *apoptosis*.

Example of growth factors

Individual growth factor proteins tend to occur as members of larger families of structurally and evolutionarily related proteins. There are dozens and dozens of

growth factor families such as TGF-beta (transforming growth factor-beta), BMP (bone morphogenic protein), neurotrophins (NGF, BDNF, and NT3), fibroblast growth factor (FGF), and so on.

Several well known growth factors are:

- Transforming growth factor beta (TGF-B)
- Granulocyte-colony stimulating factor (G-CSF)
- Granulocyte-macrophage colony stimulating factor (GM-CSF)
- Nerve growth factor (NGF)
- Neurotrophins
- Platelet-derived growth factor (PDGF)
- Erythropoietin (EPO)
- Thrombopoietin (TPO)
- Myostatin (GDF-8)
- Growth differentiation factor-9 (GDF9)
- Basic fibroblast growth factor (bFGF or FGF2)
- Epidermal growth factor (EGF)
- Hepatocyte growth factor (HGF)

Uses in medicine

For the last two decades, growth factors have been increasingly used in the treatment of hematologic and oncologic diseases like:

- neutropenia
- myelodysplastic syndrome (MDS)
- leukemias
- aplastic anaemia
- bone marrow transplantation

See also

- Signal transduction
- Receptor (biochemistry)
- Cytokine
- Angiogenesis
- Human Genome Organisation
- Growth factor receptor

External links

- MeSH *Growth+Factors*

Animal intercellular signaling peptides and proteins

Growth factors	Epidermal growth factor - Fibroblast growth factor (FGF2) - Nerve growth factor - Platelet-derived growth factor - Transforming growth factor (TGFα, TGFB, TGFB pathway)
Other	Hedgehog (Sonic hedgehog) - Integrin - JAK/STAT (JAK/STAT) - MAPK/ERK pathway (MAPK/ERK) - NF-kB - Notch (Notch 1, Notch 3) - p53 - Wnt (WNT4, Frzb)

Growth factor

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Biology Glossary search by EverythingBio.com

Definition:

A serum protein that stimulates cell division when it binds to its cell-surface receptor.

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